REMARKS

The Office Action and the cited and applied reference have been carefully studied. No claim is allowed. Claims 3-9, 11, 14 and 16 presently appear in this application and define patentable subject matter warranting their allowance. Reconsideration and allowance are hereby respectfully solicited.

The personal interview between the undersigned and Examiners Jiang and Spector on June 28, 2006, is hereby gratefully acknowledged. The undersigned wishes to thank the examiners for the courtesies extended during this interview. No agreement was reached in the discussion of proposed claims 18 and 19, which were directed, respectively, to an interferon-gamma production inducing protein encoded by a DNA sequence which hybridizes to nucleotides 85 to 281 of SEQ ID NO:1 under high stringency hybridization conditions and to one which binds to monoclonal antibody M-1 and has specific physicochemical properties. The examiners indicated that wash conditions need to be included in proposed claim 18 in order to meet the requirements of 35 U.S.C. §112. With regard to the §102(b) anticipation rejection over Nakamura et al., the examiners advised that evidence in the form of experimental results, such as difference in binding of Nakamura's factor and the presently claimed protein to monoclonal antibody M-1 or difference in

sequence or ability to hybridize to nucleotides 85 to 281 of SEQ ID NO:1 under high stringency conditions would be helpful.

Claims 3-6, 11, 14 and 16 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The examiner states that the specification does not provide support for the recitation of "having an amino acid sequence which is at least 90% homologous". This rejection is respectfully traversed.

The specification discloses an amino acid sequence of SEQ ID NO:2 in which one or more amino acids are replaced with different amino acids, one or more amino acids are added to near the N- or C-terminus of SEQ ID NO:2, or one or more amino acids at near the N- or C-terminus of SEQ ID NO:2 are deleted. These amino acid sequences have less than 100% homology to SEQ ID NO:2 (mouse IGIF or IL-18). These amino acid sequences had been easily obtainable at the time the application was filed on the basis of the disclosure of the specification and the state of the art. It is submitted that Dr. Okamura's declaration filed with the amendment dated December 1, 2005, provides support for this position.

On the other hand, as shown in "ENDOGEN Recombinant Rat IL-18", a copy of which is attached hereto, mouse IL-18 has 91.9% homology to rat IL-18 while the homologies with bovine IL-18, etc., remain less than 70%. It can be said that the recitation "having an amino acid sequence which is at least 90% homologous to ..." includes rat IL-18 but does not include bovine IL-18 etc.

Furthermore, applicants note that the examiner indicated in the Office Action dated January 24, 2006, at page 4, line 4, from the bottom:

> This is not persuasive because the issue is that the disclosed IGIF was a totally new polypeptide (emphasis added)

It is clear from this statement that the examiner *per se* considers that the present invention is directed to a totally new polypeptide. An invention directed to a totally new polypeptide should be considered as a “pioneer” invention. It is believed that a “pioneer” invention deserves wider protection than a conventional invention as highlighted in the middle of page 2 of "Prepared Remarks of James E. Rogan”, a copy of which is attached hereto.

Reconsideration and withdrawal of this rejection are therefore respectfully requested.

Claims 3-6, 11, 14 and 16 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The examiner states that the recitation in claim 3 in part (4) "possessing a

part or the whole of the amino acid sequence of SEQ ID NO:2" is indefinite because of the presence of the term "whole". This part of the rejection is respectfully traversed.

The specification discloses at page 3, third paragraph, an amino acid sequence of SEQ ID NO:2 (i.e., SEQ ID NO:3 in the original specification) in which one or more amino acids are added to near the N- or C- terminus. It is clear that the amino acid sequence corresponds to "an amino acid sequence possessing ... the whole of the amino acid sequence of SEQ ID NO:2".

The examiner also holds the recitation "but different from" in the claims to be redundant. In deference to the examiner, the recitation "but different from" is now deleted, thereby obviating this part of the rejection.

Claim 11 is further rejected as being indefinite because of the recitation "which reacts with" and "or a variant ... at least 90% homologous to". In response to this part of the rejection, claim 11 is now amended to replace the recitation "which reacts with" with "which binds to", and to delete the recitation "a sequence variant of the protein", thereby obviating the rejection. The recitation "at least 90% homologous" remains in claim 11 because applicants do not believe this recitation is indefinite as discussed above.

Furthermore, the examiner states that claim 11 defines the structure of the IGF protein by its interaction with a monoclonal antibody specific to a sequence variant of the protein, but it does not help to define the structure of the claimed protein, because such an antibody may or may not be SEQ ID NO:2 specific. However, it should be noted that claim 11 does not define the protein by its interaction with a monoclonal antibody only but also by other physicochemical properties as recited in (1) to (5) of claim 11. From this perspective, applicants believe that claim 11 is indeed definite.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

Claims 3-6, 11, 14 and 16 have been rejected under 35 U.S.C. §112, first paragraph, because the examiner states that the specification, while being enabling for claims limited in scope to the IGIF of SEQ ID NO:2 and a specific variant of said protein which has an amino acid sequence of SEQ ID NO:2 where reissue 70 is methionine or threonine, does not reasonably provide enablement for claims to a variant as defined in the claims. The same claims are further rejected under 35 U.S.C. §112, first paragraph, for lack of written description. These rejections are respectfully traversed for the reasons argued in the above new matter rejection.

Reconsideration and withdrawal of the rejections are therefore respectfully requested.

Claims 3, 5, 6, 11, 14 and 16 have been rejected under 35 U.S.C. §102(b) as being anticipated by Nakamura et al., *Infect. Immun.* 61:64-70 (1993). The examiner still considers the "factor" disclosed in Nakamura to be the same as the polypeptide of the present invention in view of Okamura's later publication, *Infect. Immun.* 63:3966-3972 (1995). This rejection is respectfully traversed.

A table is presented below which summarizes the differences between Nakamura's factor and the polypeptide of the present invention.

	polypeptide of the present invention	"factor" of Nakamura's first publication
origin	liver of mouse	serum of mouse
molecular	19,000 ± 5,000 Da (SDS-PAGE)	50,000 ~ 55,000 Da (SDS-PAGE)
activity	will not lose its activity when treated with SDS-PAGE	will lose its activity when treated with SDS-PAGE
IFN-γ inducing ability	being capable of inducing IFN-γ in IFN-γ production cells with the polypeptide alone	Being incapable of inducing IFN-γ in IFN-γ producing cells with the "factor" alone, but being capable of inducing IFN-γ in the presence of IL-2, Con-A, or anti-CD3 Mab (see Nakamura's first publication, p. 67, the second paragraph "Dual requirement and effect of a dose"

With regard to the molecular weight, it should be noted that Nakamura states at page 69, left column, lines 3-5:

> The cytokines IL-I, IL-3, IL-4, IL-5, IL-6, and tumor necrosis factor, whose molecular weight are much lower than that of the factor.

On the other hand, as shown in the reference, Fitzgerald et al. "THE CYTOKINE Facts Book", Second Edition, Academic Press, New York, 2001, pertinent pages of which are attached hereto,, the cytokines IL-1m, IL-3, IL-4, IL-5 and IL-6 have molecular weights in the range of about 17,000 to 50,000. Accordingly, the molecular weight of 50,000 to 55,000 Da of the "factor" disclosed in Nakamura, page 66, right column, third line from the bottom, is consistent with the statement above. It is therefore clear that the molecular weight of the Nakamura's "factor" is 50,000 to 55,000 (SDS-PAGE).

By contrast, the polypeptide of the present invention has a molecular weight of 19,000 ± 5,000 Da (SDS-PAGE). In general, the same substance never shows different molecular weights when measured with the same method. The examiner takes the position that Nakamura's "factor" is the same as the polypeptide of the present invention in view of the later Okamura publication. Okamura states in the paragraph bridging the left and right columns on page 3966:

> The IFN-γ producing cells in this case were NK cells, while it was unlikely that LPS

> directly stimulated NK cells (5). In our previous studies, an interleukin-12 (IL-12)-like, 75 kDa IFN-γ-inducing factor (IGIF) was observed in the sera of mice treated with *Propionibacterium acnes* challenged with LPS (16, 17). *In this study, we isolated an 18- to 19-kDa IGIF from these mice and characterized it. The serum factor whose apparent molecular weight mass was previously found to be 75 kDa by gel filtration was shown to contain the same 18- to 19-kDa IGIF.* (emphasis added)

Please note that the publication "16" cited in the above is the Nakamura publication.

Okamura teaches later in the discussion section, page 3970, right column to page 3971, left column:

> Previously, we have shown that some unidentified factor with IL-18-like activities was released into the circulation systems of bacterium-treated, LPS-challenged mice (16, 17). *In this study, we have confirmed that a similar IFN-γ-inducing factor exists in the liver extracts of such mice (Fig. 1).* This factor was purified from the liver extract and analyzed for its molecular characteristics (Fig. 2 to 4). *The molecular mass of the factor was about 18 to 19 kDa when estimated from both molecular sieving and SDS-PAGE.* Its isoelectric point determined by Mono P column chromatography was 4.8. The amino acid sequence of the NH2-terminal portion of this protein was determined and shown to be a novel protein. (emphasis added)

In view of the disclosures and teachings in Okamura, it is reasonably considered that the later Okamura publication does not assert that Nakamura's "factor" is the same as the "factor" of the later Okamura publication, but does report Nakamura's

"factor" contains "the factor having the molecular weight of 18 to 19 kDa" disclosed in Nakamura's later publication. Applicants believe it unreasonable to say that the "factor" of Nakamura is the same as the "factor" of the later Okamura publication even if the later Okamura "factor" is contained in the former Nakamura "factor".

Furthermore, applicants would like to draw the examiner's attention to Dr. Haruki OKAMURA's declaration submitted with the amendment filed December 1, 2005. Dr. OKAMURA is one of the authors of both the Nakamura reference and the later Okamura publication. In paragraph 10 of the declaration, Dr. OKAMURA states that "... we speculated that the factor could possibly be natural killer stimulatory factor (NKSF)/interleukin-12 (IL-12)". Please note that "natural killer stimulatory factor (NKSF) interleukin-12 (IL-12)" has IFN-γ inducibility (see paragraph 11 of the declaration). This statement in the declaration of Dr. OKAMURA clearly shows that even one of the authors of the Nakamura's reference *per se* did not consider the "factor" to be the polypeptide of 19,000 ± 5,000 molecular weight.

It should be emphasized that Nakamura's factor was never isolated to the protein of the present invention, even if the factor may possibly contain the protein of the present invention.

In addition, the examiner's attention is respectfully drawn to the difference between specific activities. As shown in Table 1 at page 66 of the Nakamura reference, the specific activity of Nakamura's "factor" after purification with Phenyl-Sepharose was "283,333 U/mg". By contrast, as shown in Table 1 at page 3969 of the later Okamura publication, the specific activity of the "factor" in Okamura after the same purification with Phenyl-Sepharose was only "14 U/mg". Please also note that the maximum specific activity of the "factor" of the later Okamura publication was "6,600 U/mg". If Nakamura's "factor" is the same as the "factor" of the later Okamura publication, then the specific activities of both factors should be similar after the same purification procedures. However, this is not the case. Moreover, since the later Okamura publication employs higher purification procedures than Nakamura, the maximum specific activity of the "factor" of the later Okamura publication should be higher than that of Nakamura's "factor". Again, this is not the case.

Applicants also wish to emphasize that Ushio et al., *J. Immunol.* 156:4274-4279 (1996), which is of the record as Ref. AE, report the cDNA of the "factor" having a molecular weight of 18 to 19 kDa extracted from mouse liver, i.e., the "factor" of the later Okamura publication, and does not report anything about Nakamura's "factor".

Accordingly, Nakamura does not anticipate the presently claimed invention.

Reconsideration and withdrawal of the rejection are therefore respectfully requested.

In view of the above, the claims comply with 35 U.S.C. §112 and define patentable subject matter warranting their allowance. Favorable consideration and early allowance are earnestly urged.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By /ACY/
Allen C. Yun
Registration No. 37,971

ACY:pp
624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
G:\BN\S\SUMA\Okamura2E\pto\2006-07-19amendment.doc